



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Review of Trichlorfon Incident Reports  
DP Barcode D251428, Chemical #057901, Reregistration  
Case #0104

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BACKGROUND

This addendum is provided though the Registration Eligibility Document has already been issued. This memorandum does not require any additional action, but it provided to make the data review complete.

The following data bases have been consulted for the poisoning incident data on the active ingredient Trichlorfon (PC Code: 057901):

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since

1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested.

2) Poison Control Centers - as the result of Data-Call-Ins issued in 1993, OPP received Poison Control Center data covering the years 1985 through 1992 for 28 organophosphate and carbamate chemicals. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

3) California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991) - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

## TRICHLORFON REVIEW

### I. Incident Data System

Please note that the following cases from the IDS do not have documentation confirming exposure or health effects unless otherwise noted.

Incident#3037-72

A pesticide incident occurred in 1994, when an adult male sprayed fields with trichlorfon and one week later developed headaches that lasted for three months. The timing of symptoms is inconsistent with an effect of trichlorfon unless the victim was poisoned at the time of initial exposure. No further information on the disposition of the case was reported.

#### Incident#3893-1

A pesticide incident occurred in 1996, when a 77 year old man developed a sore throat after two days of reportedly intense work with trichlorfon treated sod. No further information on the disposition of the case was reported.

#### Incident#4918-1

A lawsuit was filed concerning a death in an adult male from respiratory failure secondary to extensive diffuse alveolar damage of undetermined etiology. The death occurred following exposure to sod treated with trichlorfon. No further information on the disposition of the case was reported.

### II. Poison Control Center Data

No data was collected for the years 1985-1992 on trichlorfon. There were 54 contacts with Poison Control Centers from 1993 through 1996 concerning unintentional exposures to trichlorfon. However, only 28 of these cases received follow-up to determine medical outcome. Of the 28 cases, 18 did not develop symptoms, 9 had minor symptoms, and one case was classified as moderate. This number of cases is too small to provide meaningful comparisons with other organophosphates.

### III. California Data - 1982 through 1995

Detailed descriptions of 6 cases submitted to the California Pesticide Illness Surveillance Program (1982-1995) were reviewed. In 2 of these cases, trichlorfon was used alone and was judged to be responsible for the health effects. Trichlorfon ranked 217th as a cause of systemic poisoning in California. In one case an applicator accidentally sprayed trichlorfon into his eye while using a hand sprayer. In the second case an applicator passed through spray mist while treating a golf course. His doctor diagnosed mild exposure and symptoms of dizziness, nausea, and headache were reported. Neither

case required hospitalization or was known to take time off work due to their exposure.

#### IV. National Pesticide Telecommunications Network

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, trichlorfon was ranked 134th with 22 incidents in humans reported and 4 incidents in animals (mostly pets). From April 1995 through March 1998 the NPTN received two calls concerning human health effects possibly related to trichlorfon. Only calls where trichlorfon was the only source of exposure or where it was the only cholinesterase inhibitor and the symptoms were consistent with cholinesterase inhibition were included. The two calls involved persons who were accidentally exposed to trichlorfon. In the first case, a woman reported acute symptoms such as nausea, sweating, light-headedness, drooling, and weakness after she applied trichlorfon to her yard. In the second case, a worker developed diarrhea, abdominal cramps, headache, and nausea after the chemical spilled in his truck and he got it on his hands.

#### V. Literature reports of human poisonings

The World Health Organization (1992) included a report by Aden-Abdi et al. (1987) concerning cases that were given several doses on the same day or one day apart who experienced abdominal colic, nausea, salivation, dizziness, and headaches. Aden Abdi and Gustafsson (1989) reported on cases in rural villages in Somalia that were administered metrifonate (trichlorfon that is used to treat infection by schistosomiasis haematobium in humans). The cases were given three doses of 7.5 mg/kg on three separate days at two week intervals. The results of the study were not good since a number of patients did not follow the treatment regimen. In a later study, Aden Abdi (1990) reported on cases that were given 5 mg/kg twice in one day, which were the safest doses.

The World Health Organization (1992) included a report by Akimov and Kolesnichenko (1985) concerning 14 patients that died from acute chlorophos poisoning. They experienced congested blood vessels with perivascular edema and degeneration of the collagenous and elastic fibers of the vascular walls. "Diffuse cellular changes, such as swelling and ischemic changes, were found in the brain, spinal cord, and vegetative ganglia. There was a moderate destruction of the myelin sheaths in the lateral columns of the spinal cord and the brain

peduncles, and there were structural changes in the axons of the peripheral nerves."

The World Health Organization (1992) included a report by Batora et al. (1988) concerning a forty-two year old man who attempted suicide by ingesting 100-200 ml of 25% trichlorfon. The man was in a deep coma and had to be artificially ventilated for 37 days. His plasma cholinesterase activity was significantly decreased. Three weeks later he experienced severe weakness of the lower limbs and twenty-one months later his mobility had improved and he was able to walk by himself for a short distance.

The World Health Organization (1992) included a report by Becker et al. (1990) concerning 20 Alzheimer's patients participating in a clinical trial. The patients were administered doses of 2.5, 5, 7.5, or 15 mg/kg metrifonate every week for one to three months. A statistically significant improvement occurred for the dose of 5 mg/kg. A 60% depression in red cell cholinesterase and 80% depression in plasma cholinesterase were experienced along with minor side effects of nausea, vomiting, and/or diarrhea. At the dose level of 2.5 mg/kg, the cases did not experience any symptoms, 5 cases experienced symptoms at 5 mg/kg, 9 cases at 7.5 mg/kg, and 13 cases at 15 mg/kg each week.

The World Health Organization (1992) included a report by Csik et al. (1986) concerning 70 cases of trichlorfon poisoning (mainly suicide attempts) between 1971 and 1983. Twenty-five of the cases were re-examined in 1984 and nine (36%) of them had severe residual signs of delayed polyneuropathy and one case experienced CNS lesions. Two to three months later, four cases experienced paraesthesia and weakness of the hands but were healthy at the time of re-examination.

The World Health Organization (1992) included a report by Hayes (1982) concerning 21% of the cases that experienced polyneuropathy and other common symptoms experienced were unconsciousness and mental disturbances. The majority of the cases who experienced polyneuropathy did so three days after ingestion and up to twenty-six days later.

The World Health Organization (1992) included a report by Hierons and Johnson (1978) concerning a twenty year old man who ingested a handful of granular solid formulation which included about 80% trichlorfon. He experienced progressive neuropathy about two to eight weeks later.

The World Health Organization (1982) included a report by Kawai et al. (1982) concerning workers, who wore personal protective clothing, and applied 50% of an emulsifiable concentrate of trichlorfon to apple trees. The product was diluted a thousand-fold and applied with a speed or power sprayer. There were no significant changes in the plasma and red blood cell cholinesterase levels in the operators following either spraying. The cumulative exposure from the speed sprayer and the power sprayer per person was  $177 \pm 54.0$  mg and  $1179 \pm 398$  mg.

The World Health Organization (1982) included a report by Monson and Alexander (1984) concerning a possible human birth defect resulting from metrifonate treatment.

The World Health Organization (1992) included a report by Nordgren et al. (1981) and Davis (1986) where cases were administered doses of 7-12 mg/kg of trichlorfon. After the dosing, severe cholinergic symptoms were rarely experienced by the cases but complete plasma cholinesterase inhibition and 40-60% erythrocyte acetylcholinesterase inhibition were experienced.

The World Health Organization (1992) included a report by Shiraishi et al. (1977) concerning a 21 year old female who attempted suicide by ingesting about 50 ml of a 50% formulation of trichlorfon. She was unconscious and recovered about eight hours later. She experienced motor dominant polyneuropathy about two weeks later.

The World Health Organization (1992) included a report by Lu et al. (1984) and Hu et al. (1986) concerning occupational exposure to trichlorfon in a factory where the air concentrations exceeded  $0.5 \text{ mg/m}^3$ . The cases experienced skin contamination, decreased plasma cholinesterase levels, and changes in EEG patterns. The symptoms returned to normal after exposure ceased.

The World Health Organization (1992) included a report by Wegner (1970) concerning 6000 people, mostly in South Africa and South America, who were treated with trichlorfon for a few years to control various intestinal and body parasites. The cases were administered doses from 7.5 and up to and including 70 mg/kg. When they were given 7.5 mg/kg two to four times every two weeks, they experienced cholinesterase inhibition, weakness, nausea, diarrhea, and abdominal pain. Doses at 24 mg/kg caused the cases to experience tachycardia, salivation, colic pain, vomiting, nausea, fatigue, tremors, and sweating. All of the cases made a speedy recovery.

The World Health Organization (1992) included for reports of cases of delayed neuropathy due to trichlorfon. For example, Vasilescu et al. (1984) reported on four cases of accidental ingestion that developed a predominantly motor neuropathy three to five weeks after the initial exposure. One and a half years after treatment there was notable improvement in all cases but some signs (e.g., muscle weakness) persisted.

Czeizel et al. 1993 and Czeizel (1994) reported an incident that occurred in 1989 in Hungary, when several mothers delivered babies (11 out of 15) with birth defects (four had Down's syndrome, a prevalence rate 223 times the national rate) after they ate fish that was contaminated with trichlorfon from local fish farms. A case-control study and environmental investigations strongly suggested contaminated fish as the cause. Other likely causes such as teratogenic factors, familial inheritance, and consanguinity were ruled out. It is estimated that the mothers may have eaten 100 mg/kg during the critical period for the congenital abnormalities that were observed. Separate studies of five suicide attempts with trichlorfon found higher rates of aneuploidy in peripheral lymphocytes. The ingested dose in these suicide cases was not reported, but one case died as a result.

## VI. Conclusions

The following low effect levels have been reported in human studies:

1. In China workers exposed to 0.5 mg/m<sup>3</sup> experience reduced plasma cholinesterase (Hu et al. 1986).
2. Doses of 7.5 mg/kg given 2-4 times at two-week intervals, caused cholinesterase inhibition, weakness, nausea, diarrhea, and abdominal pain (Wegner 1970).
3. In a clinical trial weekly oral doses (for 1-3 months) of 5 mg/kg led to 60% depression of red blood cell cholinesterase and 80% depression of plasma with symptoms of nausea, vomiting, and/or diarrhea in some patients. No significant effects, were reported at 2.5 mg/kg, however.
4. Though not conclusive, strong evidence from Hungary suggests birth defects in women ingesting 100 mg/kg of trichlorfon.

Relatively few incidents of illness have been reported due to trichlorfon based on the Incident Data System, Poison Control Center Data, or the California Pesticide Illness Surveillance Program. According to the above literature reports where humans were

administered doses of trichlorfon, 5 mg/kg was the associated dose with persons experiencing symptoms such as red cell cholinesterase, plasma cholinesterase depression, nausea, vomiting, and/or diarrhea.

## VII. Recommendations

Measures to reduce risk to applicators and handlers of trichlorfon should be consistent with other organophosphate and carbamates. All food uses of trichlorfon have already been canceled.

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